



## Review article

## Brain vascular changes in adults with congenital heart disease: A systematic review

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## ABSTRACT

Less information is available on brain integrity in adults with congenital heart disease than on brain changes in newborns and children with heart defects. Nevertheless, the number of adults with congenital heart disease is increasing rapidly and it has been shown that adults with congenital heart disease develop dementia almost twice as frequently as adults in the general population.

In the context of a rapidly growing congenital heart disease population, neuroradiological-oriented investigations of biomarkers distinctive for vascular damage, brain aging, and possible cognitive impairment is a crucial challenge. We provide an overview of the existing literature on neuroimaging studies in adults with congenital heart disease and discuss methodology issues to further investigate this subject. Overall, we aim to raise awareness of the importance of brain health studies in adults with congenital heart disease given the likely increasing impact on social and healthcare systems.

## 1. Background

Congenital heart disease (CHD) affects almost one out of 100 live-births with similar prevalence around the world (Triedman and Newburger, 2016). About 90% of patients with complex CHD (i.e. atrioventricular septal defect, interrupted or hypoplastic aortic arch, pulmonary atresia, truncus arteriosus communis, totally anomalous pulmonary venous drainage, transposition of great arteries, tetralogy of Fallot and univentricular heart) survive into adulthood thanks to the advancement of surgical and medical care. As a consequence, there are now more adults with CHD (ACHD) than children with CHD (Triedman and Newburger, 2016). Adequate management of this new population requires comprehensive evaluation of the effect of ACHD on patients' aging and possible comorbidities as well as on the potential long-term impact of related treatments (Marelli et al., 2016). Among potential comorbidities, brain vascular changes may be a direct complication of CHD. A large retrospective multicentric study (including 23,153 patients) reported an incidence of cerebrovascular accidents in CHD

subjects up to 100 times higher than that observed in healthy subjects of comparable age (Hoffmann et al., 2010). A recent Danish population-based cohort study has reinforced concern over the risk of cerebrovascular disease in describing a twofold higher risk of developing dementia of all-types for those with complex CHD (Bagge et al., 2018). Indeed, the hazard ratio (HR) for early-onset dementia (< 65 years of age) was 2.6 (95% confidence interval [CI], 1.8–3.8) when considering all CHD diagnostic groups compared with controls (Bagge et al., 2018). When statistical correction for comorbidities (acquired cardiovascular disease and diabetes mellitus) was performed, ACHD still carried a slightly higher risk for developing dementia than healthy subjects (HR = 1.48, 95% CI (1.11–1.97)). According to the authors, a possible explanation might center on a multifactorial altered brain reserves, i.e. decreased tolerance to brain aging changes (Bagge et al., 2018), in which brain vascular disease is expected to prevail over the effects of neurodevelopmental abnormalities as patients with CHD get older (Marelli et al., 2016). In this regard, it is known that patients with CHD show signs of brain immaturity already at birth and demonstrate poorer

**Abbreviations:** ACHD, adults with congenital heart disease; ASL, arterial spin labelling; CBF, cerebral blood flow; CHD, congenital heart disease; CI, confidence interval; CMBs, cerebral microbleeds; cSVD, cerebral small vessel disease; HR, hazard ratio; IQR, interquartile range; NAWM, normal appearing white matter; SD, standard deviation; WMH, white matter hyperintensities; STAGE, strategically acquired gradient echo

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**Table 1**  
Data extracted from the study included in this review.

Study	ACHD type of	Patient enrollment	Control group	Patients undergoing MRI	Exclusion criteria	ACHD sample age (years)	ACHD sample males n (%)	Brain features	Measurement scale
<a href="#">Horigome et al. (2006)</a>	Unrepaired cyanotic	Prospective	Yes <sup>a</sup> (n = 9)	15	Patients with history of stroke, procedure related cerebrovascular event, brain abscess, or atrial fibrillation or with a prosthetic valve. Contraindications for MRI.	18–45, M = 24	NA	Silent chronic cerebral infarcts; cortical atrophy; intracranial circulation	Counts
<a href="#">Cordina et al. (2014)</a>	Unrepaired cyanotic	Prospective (patients) and retrospective (controls)	Yes (n = 10)	10	Patients with major physical or intellectual impairment. Contraindications for MRI.	40 (m) ± 4 (SE)	7 (70%)	GM, WM and CSF volumes, cortical thickness, WMH (Scheltens scale), intracranial circulation, lacunes, ventricles morphology	Qualitative, counts and quantitative
<a href="#">Jensen et al. (2015)</a>	Unrepaired cyanotic	Prospective (patients)	No	72	NA	40 (m) ± 14 (SD)	43 (44%) <sup>b</sup>	Acute and chronic cerebral infarcts, WMH count	Counts
<a href="#">Sluman et al. (2017)</a>	Repaired Tetralogy of Fallot	Prospective (patients)	No	64	Patients with chromosomal disorders. Contraindications for MRI.	20–69, M = 37	30 (47%)	Cerebral infarcts, WMH volume	Counts and quantitative
<a href="#">Chai et al. (2018)</a>	Repaired Tetralogy of Fallot	Prospective (patients)	No	46 <sup>c</sup>	Not Reported (extracted from <a href="#">Sluman et al. (2017)</a> )	23–69, 37.4 (m) ± 14.0 (SD)	22 (48%)	WMH count, cerebral blood flow	Counts and quantitative
<a href="#">Codari et al. (2018)</a>	Repaired Tetralogy of Fallot	Prospective (patients and controls)	Yes (n = 10)	10	CNS disease, previous brain surgery, patent oval foramen. Contraindications for MRI.	22–64, M = 45 IQR 30.5–49.5	6 (60%)	WMH volume, cerebral microbleeds	Quantitative and counts

Abbreviations: m = mean; M = median; SD = standard deviation; IQR = interquartile range; GM = gray matter; WM = white matter; WMH = white matter hyperintensities; CSF = cerebrospinal fluid; CNS = central nervous system.

<sup>a</sup> Controls do not undergo MRI.

<sup>b</sup> Numbers refer to the whole study sample of 98 ACHD which comprises 72 patients (% for male and female unknown) undergoing MRI.

<sup>c</sup> FLAIR images processed in 36 subjects only due to motion artefacts.

neurodevelopmental scores later on (Mebius et al., 2017). Infants with CHD show a low preoperative cerebral blood flow (Licht et al., 2004) and a high incidence of white matter abnormalities, similar to that reported in preterm newborns. Both populations suffer from hypoxic-ischemia injury with possible impaired delivery of energy substrates, oxidative stress, and pro-inflammatory states, exacerbated in CHD by the presence of cardiopulmonary bypass (Miller and McQuillen, 2007). Brain dysmaturation together with genetic and epigenetic alterations may account for the adverse, albeit heterogeneous, motor and functional outcomes observed in children and adolescents who undergo repair of complex CHD. In this context, brain MRI studies in these young patients are intended to discriminate between those deficits resulting from genetic abnormalities, in particular brain development in fetal life, and postnatal injuries, in particular those associated with surgical procedures (Marelli et al., 2016).

In adults, early onset of cardiovascular risk factors for brain injury such as, among others, hypertension, metabolism disorders and dysrhythmia, together with an increased incidence for ischemic and hemorrhagic stroke, may impact the brain and contribute to precocious neurocognitive decline in ACHD (Lanz et al., 2015; Marelli et al., 2016). The brain in CHD patients is primed for vulnerability to insults. As the cardiovascular disease burden shifts from those factors associated with the heart disease itself to acquired cardiovascular comorbidities, the decreasing gradient of neurodevelopmental abnormalities is replaced by an increasing gradient of neurovascular disease (Marelli et al., 2016).

In spite of the clear association between CHD and acquired vascular brain changes, in-depth knowledge on the evolution of neurocognitive functions and correlated imaging biomarkers of brain vascular damage in ACHD is currently lacking. Herein, we present a summary of literature reports aimed at investigating this association.

## 2. Materials and methods

### 2.1. Search strategy and eligibility criteria

In January 2019, a systematic search was performed using MEDLINE (PubMed, [www.pubmed.gov](http://www.pubmed.gov)) for neuroimaging investigations of adults with congenital heart disease. The search query was: (brain volume[Title]) OR magnetic resonance imaging of the brain [title]) OR cortical thickness[Title]) OR cerebral blood flow[Title]) OR cerebral damage[Title]) OR brain damage[Title]) OR brain aging [Title]) OR cerebral and pulmonary thrombosis[Title])) AND (tetralogy of Fallot[Title] OR congenital heart disease[Title])). The search was limited to original articles published in English in peer-reviewed journals with an available abstract. Studies on fetuses, newborns, children and adolescents were excluded. No limits were applied regarding publication date.

The initial screening of eligible articles was performed, based only on title and abstract, by two independent readers. Eligible articles were those that reported in the abstract qualitative or quantitative brain features obtained through neuroimaging in adult patients with congenital heart disease. The full text of all eligible articles was thereafter

evaluated. Finally, the reference lists of the included articles were hand-searched for additional eligible studies.

### 2.2. Data extraction

We extracted the journal name, year of publication, study design, and numbers of patients and controls for each included article. We also extracted the type of CHD and the demographic details of the patient group. Moreover, we reported magnetic field strength, MRI protocol and brain imaging features. We provided descriptive statistics for numerical variables and qualitative descriptions for nominal variables like MRI protocols and brain features.

## 3. Results

### 3.1. General overview

From the initial search, 14 articles were retrieved of which 5 were eligible for inclusion. One additional article was retrieved from the reference lists of the 5 selected articles. All six articles had a cross-sectional design with prospective patient enrollment. The number of enrolled ACHD subjects ranged from 10 (Codari et al., 2018; Cordina et al., 2014) to 72 (Jensen et al., 2015) with a median value of 31 subjects and a interquartile range (IQR) of 11–60 subjects. Inclusion and exclusion criteria for patients' eligibility among the studies were heterogeneous (Table 1) or even not specified (Jensen et al., 2015).

A control group was absent in three of the six articles (Chai et al., 2018; Jensen et al., 2015; Sluman et al., 2017). The age of the enrolled ACHD patients ranged from 18 years (Horigome et al., 2006) to 69 years (Sluman et al., 2017). However, due to the heterogeneity of the reported results, descriptive statistics were not performed for this variable. Table 1 summarizes the information extracted from the included studies.

The image modality of choice was always MRI. The magnetic field strength was 1.5 T in three studies (Codari et al., 2018; Cordina et al., 2014; Horigome et al., 2006) and 3 T in the remaining studies (Chai et al., 2018; Jensen et al., 2015; Sluman et al., 2017). Detailed characteristics of the MR sequences used are presented in Table 2.

### 3.2. Main findings

Horigome et al. reported on 15 ACHD patients that had not undergone cardiopulmonary bypass or catheter interventions. Seven (47%) patients showed MRI signs of chronic brain infarctions, which were visible as lesions characterized by low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. Three patients also showed diffuse cortical atrophy. One-way ANOVA revealed statistically significant differences in terms of packed cell volume ( $p = .016$ ), protein C activity ( $p = .002$ ) and oxygen saturation ( $p < .001$ ) between healthy subjects and patients. A post-hoc analysis revealed lower oxygen saturation ( $77.9\% \pm 5.8\%$  vs.  $88.0\% \pm 6.6\%$ ,  $p < .005$ ); higher packed cell volume ( $63.2\% \pm 7.6\%$  vs.  $54.3\% \pm 7.3\%$ ,  $p < .05$ ); and reduced protein C activity

**Table 2**  
Magnetic field strength and sequence protocols adopted in studies investigating brain MRI in ACHD patients.

Study	Field strength	T1-weighted	T2-weighted	FLAIR	MRA	T2*-weighted	DWI	ADC	Perfusion
Horigome et al. (2006)	1.5 T	✓	✓	✓	✓	–	–	–	–
Cordina et al. (2014)	1.5 T	✓	–	✓	✓	✓	✓	–	–
Jensen et al. (2015)	3 T	✓	✓	✓	✓	✓	✓	✓	–
Sluman et al. (2017)	3 T	Protocol not reported							
Chai et al. (2018)	3 T	✓	–	✓	–	–	–	–	✓
Codari et al. (2018)	1.5 T	✓	–	✓	–	✓	–	–	–

Abbreviations: ACHD = adults with congenital heart disease; FLAIR = fluid-attenuated inversion recovery; MRA = magnetic resonance angiography; DWI = diffusion-weighted imaging; ADC = apparent diffusion coefficient; ASL = arterial spin labeling.

(65.6%  $\pm$  15.9% vs. 88.7%  $\pm$  3.4%,  $p < .05$ ) in patients with brain MRI abnormalities compared to patients with normal brain MR images (Horigome et al., 2006).

Cordina et al. evaluated brain MRI features in ACHD patients without any history of stroke or neurological deficits. Imaging and blood sampling analysis were performed on ten cyanotic ACHD patients with unrepaired defects. Aside from generalized global gray and white matter volume reduction, cortical gray matter was symmetrically thinned in the dorsolateral prefrontal cortex. The cortical thickness showed a significant negative correlation with serological biomarkers of inflammation linked to heart failure such as high sensitivity C-reactive protein ( $R = -0.964$ ,  $p < .0001$ ), endothelial dysfunction (asymmetric dimethylarginine,  $R = -0.75$ ,  $p = .026$ ) and neuro-hormonal activation (brain natriuretic peptide,  $R = -0.89$ ,  $p = .009$ ). No significant correlation was noted between MRI brain volume measures and oxygen saturations, packed cell volume and viscosity. In addition, lacunar infarcts were observed in nine patients. Finally, the white matter hyperintensities (WMH) burden was also found to be high at semi-quantitative assessment. Peculiarly, four patients displayed multiple subcortical (cerebellar) lacunes (Cordina et al., 2014).

Jensen et al. investigated pulmonary and cerebral thrombosis in ACHD patients assessed through multimodal imaging. Seventy-two cyanotic ACHD patients (40.0  $\pm$  14.0 years) with residual unidirectional or bidirectional shunts and oxygen saturation (83%  $\pm$  7%) underwent brain MRI. While 34/72 patients showed lacunar and/or cortical signs of previous stroke, only 7/72 (10%) patients presented with a history of stroke. The remaining 27 patients were considered to have silent brain infarcts. A high prevalence of WMH (47/72 patients, 65%) was also reported (Jensen et al., 2015).

Sluman et al. reported on brain damage in patients with repaired ACHD. An increased mean volume for discrete foci of WMH was noted in patients (469 mm<sup>3</sup>  $\pm$  960 mm<sup>3</sup>) than in controls (188 mm<sup>3</sup>  $\pm$  258 mm<sup>3</sup> retrieved from a previously published database (Neema et al., 2009)). Furthermore, a higher frequency of cerebral infarcts was observed in 64 patients with Tetralogy of Fallot (age 38.5  $\pm$  10.5 years) that underwent cardiac and brain MRI than in the general population. The prevalence of cerebral infarcts was 19% ( $n = 12$ , seven cortical and five subcortical infarcts). Neuropsychological testing revealed cognitive impairment in 21 patients (32% of the study sample), mostly affecting areas related to language and executive functioning (Sluman et al., 2017).

Chai et al. performed quantitative analysis of cerebral blood flow (CBF) using arterial spin labeling (ASL) in 46 adult patients with repaired Tetralogy of Fallot (age 37.4  $\pm$  14.0 years; mean  $\pm$  SD) (Chai et al., 2018). WMH was found in 83% ( $n = 30$ ) of 36 subjects on which assessments were made. Logistic regression analysis revealed significant correlations between WMH burden and age at first surgery ( $p < .010$ ), body mass index ( $p < .050$ ) and patient age ( $p < .05$ ). Moreover, the year of first surgery and age remained independent predictors of WMH presence at multivariate analysis (combined  $R^2 = 0.44$ ). Regarding cerebral perfusion in different vascular territories, the difference in CBF between areas of normal appearing white matter and WMH were only borderline significant ( $p = .070$ ) (Chai et al., 2018).

Finally, a proof-of-concept study by Codari et al. investigated early signs of brain aging in ACHD through the evaluation of imaging signs of cerebral small vessel disease (cSVD) in 10 adult patients with repaired Tetralogy of Fallot (median age 45.0 years; range 22–64 years). The authors noted a high number of cerebral microbleeds (CMBs) in the patient group (6.0 [4.0–7.8]; median and [IQR]) and no CMBs at all in an age and sex-matched control group ( $p = .002$ ). However, no significant correlation was found between the presence of CMBs and the number of surgical interventions with cardiopulmonary bypass ( $\rho = 0.384$ ,  $p = .273$ ). Moreover, a significant positive correlation ( $\rho = 0.80$ ,  $p = .005$ ) was found between WMH burden and New York Heart Association (NYHA) functional classification (Codari et al.,

2018).

#### 4. Discussion

In 2006, Horigome et al. (Horigome et al., 2006) performed the first neuroimaging investigation on ACHD. The lower arterial oxygen saturation and higher hematocrit observed in the patient group allowed the authors to postulate a link between reactive erythrocytosis and cerebrovascular accidents (Horigome et al., 2006). They suggested that chronic hypoxemia and a resulting increase in hematocrit may have caused cerebral infarctions in patients with ACHD with uncorrected heart disease. An impact on the coagulation system, namely suppression of the thrombomodulin-protein C-protein S system, was suggested by a significant reduction in protein C activity in ACHD patients with brain MRI abnormalities compared with ACHD patients without abnormal MRI findings. This may have resulted from primary downregulation of the coagulation system due to chronic vessel injury from hyperviscosity, hypoxemia, and consumption of coagulation factors and platelets. The authors noted multiple and scattered subclinical ischemic lesions to support the abovementioned mechanisms (Horigome et al., 2006).

In 2014 Cordina et al. (Cordina et al., 2014) reported quantitative measures of brain features in patients with ACHD. Their results revealed focal reduction of the dorsolateral prefrontal cortex, which is involved in cognitive processes related to executive functions. According to the authors, vascular injury due to inflammation, endothelial dysfunction, and neuro-hormonal activation was considered to underpin the observed loss of gray matter. In contrast with the previous report, oxygen saturation and blood viscosity were not correlated with any of the measures of brain volume.

In 2015, Jensen et al. (Jensen et al., 2015) used multiple imaging modalities to investigate cerebral and pulmonary thrombosis in patients with cyanotic congenital heart disease. Complexity of the heart disease and low oxygen saturation were both found to be significant risk factors for cerebral infarction. Overall, the study looks at thromboembolism as a potential pathogenetic mechanism in determining either symptomatic or subtle brain pathological changes. Specifically, the authors did not find any statistical significance for the association between hemostatic imbalance or reactive erythrocytosis and cerebral thrombosis, suggesting that ischemia rather than thromboembolism could underpin the MRI findings reported. According to the authors, the high number of brain infarcts located in the subependymal area and the increased WMH burden support the ischemic-driven argument (Jensen et al., 2015).

Recently, Sluman et al. (Sluman et al., 2017) reported a lower prevalence of cerebral infarcts in cyanotic ACHD patients than had previously been described (Horigome et al., 2006; Jensen et al., 2015). In their studies, brain damage was significantly related to patient age and age at first surgery, in agreement with the hypothesis that prenatal and ante-surgical brain injury play a crucial role for subsequent brain parenchymal integrity. Interestingly, no statistically significant difference was found in the number of surgeries between patients with abnormal MRI findings and those without. Consequently, cardiac surgery could not be held entirely responsible for the pathological neuroimaging findings observed, indicating possibly different, unconsidered etiologies. Moreover, the observed cognitive impairment mainly affecting language and executive functioning support the imaging findings reported by Cordina et al. (Cordina et al., 2014) involving thinned cortical thickness of the dorsolateral prefrontal cortex.

Chai et al. emphasized the statistical significance of age at first surgery as a possible predictor for WMH, supporting the findings of Sluman et al. (Sluman et al., 2017), concerning the change in surgical techniques and patient management that occurred during the second half of the last century (Apitz et al., 2009). As possible pathogenic explanations for vascular changes in adults with repaired cardiac disease, the authors took into account perinatal and preoperative cyanosis, surgical damage and predisposition to chronic cerebral microvascular disease, namely accelerated vascular aging (Chai et al., 2018).



In addition to the above mentioned brain features, cerebral microbleeds are biomarkers of cSVD and tend to increase with age (Poels et al., 2011). Even though a cardiopulmonary bypass constitutes a potential leading cause of CMB occurrence (Kim et al., 2017), Codari et al. did not observe significant correlations between CMB counts in patients with Tetralogy of Fallot and the number of surgeries and/or number of cardiac procedures with cardiopulmonary bypass. According to the authors, the high CMB burden observed in their patient sample is an indirect sign of vascular damage and blood brain barrier leakiness in patients with ACHD (Codari et al., 2018).

Half of the studies investigated vascular brain changes in Tetralogy of Fallot patients due to their high risk for developing all-cause dementia. Indeed, according to Bagge et al., Tetralogy of Fallot patients had a hazard ratio for all-type dementia of 2.25 when compared with the general population, the highest among all CHD groups (Bagge et al., 2018).

The pathophysiology of the imaging findings reported in the examined studies constitutes an open issue. Apart from cerebrovascular damage, the increased cerebral vessel disease burden observed could be mediated by a combination of genomic vulnerability, brain dysmaturation, heart surgery and acquired cardiovascular diseases, together resulting in blood-brain barrier disruption and subsequent MRI-detectable changes (Codari et al., 2018). A disrupted blood-brain barrier causes extravasation of plasma components and cells, leading to initiation or progression of WMH as well as macrophage and microglia engulfment with hemosiderin and occurrence of microbleeds (Codari et al., 2018).

Even though long-term longitudinal data are missing, we may postulate that the findings observed in adults may not match those seen in infants undergoing heart surgery. Indeed, white matter injuries in children have been shown to regress at MRI performed 3 months after cardiac procedures (Beca et al., 2013), while cerebral microbleeds might evolve or more seldom disappear (Poels et al., 2011). That is to say, the imaging findings observed constitute the evolving result of a cumulative burden of biological aging and cerebrovascular damage that cannot be extensively explained by perinatal injury and heart surgery alone.

The evaluated studies represent the first attempts at understanding imaging-based vascular brain sequelae in patients with ACHD. In our opinion, this topic should be investigated more thoroughly. Unfortunately, the heterogeneity in terms of study design prevents us from drawing conclusions. Small samples limit three studies (Codari et al., 2018; Cordina et al., 2014; Horigome et al., 2006). Moreover, three others focused on patients with ACHD with uncorrected defects or residual shunts (Cordina et al., 2014; Horigome et al., 2006; Jensen et al., 2015), meaning that chronic hypoxemia or paradoxical embolization could be responsible. Notably, Cordina et al. (Cordina et al., 2014), Sluman et al. (Sluman et al., 2017), Chai et al. (Chai et al., 2018), and Codari et al. (Codari et al., 2018), quantified MRI findings of brain damage whereas Horigome et al. (Horigome et al., 2006) performed only qualitative analysis, while Jensen et al. (Jensen et al., 2015) merely estimated the prevalence of cerebral lesions. A further issue is that control groups were lacking (Chai et al., 2018; Jensen et al., 2015) or were retrieved from previously published datasets (Sluman et al., 2017). The latter constitutes a relevant source of bias when dealing with unstandardized procedures for estimation of biomarkers. Whereas WMH are widely used as imaging biomarkers of cSVD, their assessment can be biased. Indeed, the lack of standardization of image acquisition protocols and post-processing, together with scanner technical differences and the magnitude and scale variability of MRI signal intensities across different experimental setup, hinders the reproducibility of the segmentation process.

Brain MRI protocols used in ACHD patients mainly focus on morphological imaging. T1-weighted, T2-weighted, fluid-attenuated inversion recovery, T2\*-weighted or susceptibility-weighted, and diffusion-weighted sequences should be performed according to

standardized research protocols (Wardlaw et al., 2013). Nevertheless, the use of advanced MRI approaches may improve the characterization of vascular brain changes in ACHD patients, in particular those occurring in normal-appearing white matter (NAWM) of subjects presenting with WMH.

Several studies on children with CHD employed different MRI sequences to assess vascular brain damage beyond morphology. Such sequences included magnetic resonance spectroscopy, and diffusion and perfusion imaging (Miller et al., 2007). However, only a few studies investigated the value of these techniques in ACHD patients (Chai et al., 2018; Cordina et al., 2014; Horigome et al., 2006).

In adults, neuroimaging should be able to differentiate past global lesion burden from present chronic ongoing cerebrovascular disease, and possibly to estimate the risk of future cerebrovascular accidents. Measures of past global lesion burden (congenital and infancy-acquired vascular insults) should focus on quantitatively assessing malacic lesions (lacunes, small brain infarcts) and CMBs, as well as volumetry of total gray matter and white matter.

Measures of adult chronic ongoing cerebrovascular disease are mainly based on gliotic lesions (WMH), and today can rely on microstructural parameters offered by diffusion imaging, using classical diffusion tensor imaging parameters (mean diffusivity, fractional anisotropy, radial and axial diffusivity), or even more advanced two-shells models such as neurite orientation dispersion and density imaging. Indeed, diffusion tensor imaging and its derived parameters such as fractional anisotropy and mean diffusivity allow microstructural changes in the white matter to be evaluated (Maniega et al., 2015; Wardlaw et al., 2013). Reduced values of the former and increased values of the latter have been observed in WMH when compared with normal-appearing white matter (Bastin et al., 2009). On the other hand, a snapshot of current ongoing perfusional brain status today may be assessed by measuring absolute cerebral blood flow by ASL. As well known for large vessels and small vessel disease, cerebrovascular risk factors, including decreased cardiac output, may cause global or regional perfusional deficit and are likely to predispose brain to future ischemic lesions.

Finally, diffusion parameters of microstructural damage and perfusion parameters of functional deficit can also be simultaneously obtained by a promising acquisition method, the so-called intravoxel incoherent motion imaging technique (Wong et al., 2017).

Moreover, quantitative maps, in addition to those obtained with diffusion-weighted protocols, may improve white matter characterization. Longitudinal relaxation time (T1), a quantitative estimate of brain water content, may also be a useful technique to detect increased water content in WMH and in the encompassing NAWM (Bastin et al., 2002; Maniega et al., 2015; Muñoz Maniega et al., 2017). Furthermore, alteration in susceptibility may characterize the myelin damage that occurs as the brain ages. Indeed, susceptibility values change with age. In particular, a recent study reported that white matter susceptibility values of three major fiber groups (i.e. internal capsule, splenium of corpus callosum and optic radiation) decrease during brain development and maturation, and slightly increases during brain aging (Li et al., 2014).

Usually, quantitative and qualitative MRI is performed with multiple scans. Such comprehensive MRI protocols require long acquisition times, even on the most recent MRI equipment. The introduction of innovative techniques may enable faster examinations. An example is provided by the strategically acquired gradient echo (STAGE) protocol, which provides whole brain qualitative and quantitative MRI data suitable for the quantification of vascular brain changes with a limited acquisition time (Chen et al., 2018; Wang et al., 2018).

Future studies should focus on large samples of clinically stable repaired ACHD subjects to assess quantitatively the vulnerability for brain damage, trying to avoid confounding variables. It is crucial to design cross-sectional and longitudinal studies in which imaging and both neurocognitive and psychological testing are performed at the

same time points. The strong evidence for a high risk of psychological and social functioning impairment resulting from longitudinal population-based studies in ACHD calls for the investigation of neuroimaging correlates of those functional parameters (Zomer et al., 2012).

## 5. Conclusion

To summarize, ACHD patients constitute a young and increasing population (Engelfriet et al., 2005). Patients come with a marked risk of cerebrovascular accidents and may have cognitive drawbacks across their lifespan (Marelli et al., 2016). Since acquired cardiovascular risk factors may play a prominent role in determining the high propensity towards developing dementia in ACHD, it would be advisable to strictly monitor the brain health of these patients with thorough neuroimaging protocols and, where possible, to prevent and intervene on those factors possibly responsible for causing cerebrovascular accidents and eventual cognitive decline. In this sense, future studies should open the way for predictive models based on the correlation between brain MRI vascular biomarkers and cognitive functions in this target population, with the aim of developing tailored preventive strategies to increase their quality of life. We stress the need for a more comprehensive view on the implications for the brain, initially via neuroimaging tools. We hope for a change in the approach to this peculiar category of patients, whose health goes far beyond heart defect care.

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## Declarations of interest

None.

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